REMARKS

Reconsideration of the present application in view of the present amendment and the following remarks is respectfully requested. Claims 1-40 were pending, claims 12-26 and 35-40 previously having been withdrawn from consideration, with the further previous election having been made of the species identified as "Cpd. No. 1" for examination of the recited genus "agent that selectively impairs a mitochondrial calcium/ sodium antiporter activity." Applicants request, by entry of the amendment submitted herewith, cancellation of claims 12-26 and 35-40 without prejudice, solely for purposes of advancing the prosecution of this application after final rejection. Accordingly, claims 1-11 and 27-34 are currently under examination. Claims 1-4 have been amended solely for purposes of moving the application forward to allowance, without acquiescence in any rejection of record, by incorporating the subject matter of claim 25, now canceled. Claims 2-4, 27-29 and 34 have been amended to more particularly point out and distinctly claim subject matter which applicants regard as the invention, and to correct improper dependencies on claims for which cancellation is requested herewith. No new matter has been added.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-11 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. More specifically, the PTO concedes that the specification is enabling for Cpd. No. 1 but alleges that with regard to other compounds, "applicants merely describe what applicants want the compounds to do, but not the actual compounds themselves through a recitation of functional language, i.e., an agent that can impairs (*sic*) the mitochondrial calcium/sodium antiporter (MCA) activities." (Action, page 5, lines 3-6). The PTO also asserts that the scope of the disclosure enabled by the specification is not commensurate with the scope of the claims.

Applicants respectfully traverse these grounds for rejection. The present invention is directed in pertinent part to a method for treating diabetes mellitus, comprising administering, to a subject having or being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a

mitochondrial calcium/sodium antiporter activity in an insulin secreting cell wherein the agent has the recited structure according to the amendment submitted herewith, and to related methods.

Applicants respectfully point out that, contrary to the assertion in the Action (page 5, lines 1-3) and for reasons previously made of record, it cannot be doubted that at the time of filing the instant application, applicants were in possession of compounds that possessed the "structural/functional characteristics for the specific claimed activities". As noted above, the PTO has conceded that the invention is enabled for Cpd. No. 1, a representative species previously elected from within the genus of compounds recited for use in the claimed methods.

In fact, the instant specification discloses multiple syntheses of Cpd. No. 1 (*e.g.*, Examples 1, 2) as well as of more than 20 additional compounds within the recited genus (*e.g.*, Example 3), and provides characterization of the properties of a majority of these compounds (*e.g.*, Example 4). Inhibition of mitochondrial calcium/ sodium antiporter activity by such compounds is shown, for example, in Examples 6 and 9, and promotion of enhanced insulin secretion by insulin secreting cells in the presence of such compounds is described, for instance, in Examples 5, 7 and 10. Applicants therefore respectfully submit that the PTO errs in its assertion that the enablement requirement of 35 U.S.C. §112, first paragraph has not been met, where in the instant application there is no lack of the "reasonable detail" which "must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir.), *cert. denied*, 522 U.S. 963, 139 L. Ed.2d 310, 118 S. Ct. 397 (1997) (quoting *Brenner v. Manson*, 383 U.S. 519, 536, 16 L.Ed.2d 69, 86 S. Ct. 1033 (1966)).

Accordingly, and for reasons also previously made of record, applicants submit that even without the amendment submitted herewith, the instant specification enables a person skilled in the art to make and use the claimed invention readily and without undue experimentation. Nevertheless, and solely for purposes of advancing prosecution of the present application without prejudice to any related applications directed to similar subject matter, applicants request entry of the present amendment and acknowledgment of the allowability of the concededly enabled method directed to the use of the elected species Cpd. No. 1, as well as

examination and acknowledgment of the allowability of subject matter directed to the use of other species of agents within the recited genus.

Therefore, applicants respectfully submit that the instant specification and claims satisfy the requirements for enablement under 35 U.S.C. § 112, first paragraph. Accordingly, applicants respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-11 stand rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. More specifically, the PTO is unclear regarding the meanings of the recitations "a subject having or suspected of being at risk for having diabetes mellitus" and "agent that . . . impairs mitochondrial calcium/ sodium antiport (*sic*) activity". In particular, it is asserted in the Action (page 6, lines 18-20) that, "For a subject to be in risk of having diabetes, he/she *has to be diagnosed* to have certain signs and symptoms", (emphasis added) and also that, "For a subject that is suspected to be at risk of having diabetes, *no diagnosis is required* to be made" (emphasis added). Based on these assertions, the PTO alleges that the metes and bounds of the claims are not clear.

Applicants respectfully traverse these rejections and submit that the meaning of the claims is clear, and that the instant application fully complies with the requirements of 35 U.S.C. §112, second paragraph.

With regard to "suspected of being at risk", applicants submit that the PTO apparently ignores the disjunctive "or" which, in the instant claims, constructively separates the recitation "a subject *having* diabetes mellitus" from the recitation "a subject *suspected of being at risk for having* diabetes mellitus" (emphases added). The PTO errs in its assertion that, "For a subject to be in risk of having diabetes, he/she *has to be diagnosed* to have certain signs and symptoms" (emphasis added). On the contrary, the specification makes clear that a subject "having diabetes mellitus" as recited in the instant claims may have been diagnosed as a diabetic according to one or more art-accepted criteria, for reasons previously made of record, and also

makes clear that "a subject suspected of being at risk for having diabetes mellitus" need not have been definitively diagnosed.

Applicants submit that in view of the instant application, persons skilled in the relevant art well know that there can be any number of risk factors for diabetes which may provide a reasonable basis for suspecting that a subject may be at risk for diabetes, but which risk factors do not amount to a diagnosis from which it may be concluded that the subject in fact has diabetes. For example, the present specification (*e.g.*, page 1, lines 15-22) describes a genetic basis upon which a subject may be suspected of being at risk for having diabetes solely by being related to an afflicted individual. This genetic basis is a risk factor, but it is not a diagnosis, and from this factor the meaning of "a subject suspected of being at risk for having diabetes" is clear, *i.e.*, despite the presence of the risk factor (a diabetic relative) the subject may well have no greater risk for having diabetes than any other randomly selected individual; hence the subject can only be "suspected" of being at risk for having diabetes. As another example, the specification (*e.g.*, page 1, line 23 through page 2, line 10) describes certain phenotypes which are not diagnostic for diabetes *per se*, but which, if present in a subject, could signify that a skilled person might suspect that the subject could be at risk for having (or later developing) diabetes even where a diagnosis of diabetes has not been made, and even where presence of the phenotype does not necessarily increase the risk of having diabetes, but only increases the suspicion that such risk may be present.

Nevertheless, without acquiescence in the rejection and solely to advance prosecution of the present application after final rejection by placing it in condition for allowance, the recitation "suspected of" has been deleted from claims 1-4 such that upon entry into the record, the rejections of these claims are obviated. Accordingly, applicants submit that the application as amended herewith fully complies with the requirements of 35 U.S.C. § 112, second paragraph, and request that the rejections be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-11 and 27-34 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Kennedy et al. (1996 *J. Clin. Invest.* 98:2524) and Cox et al. (1993 *Trends Pharmacol. Sci.* 21:595). The PTO asserts that Kennedy et al. teach dependency of insulin secretion on cellular glucose levels and related elevation of cytosolic and intramitochondrial Ca2+ levels, such that a skilled artisan would recognize increased insulin levels in response to elevated glucose as a treatment for diabetes. The PTO asserts further that Cox et al. teach that the elected compound, CGP-37157 (Cpd. No. 1 in the instant application), is a mitochondrial Na+/Ca2+ exchanger antagonist that would be expected to increase intramitochondrial Ca2+ concentration, but concedes that the references fail expressly to teach CGP-37157 as an oral diabetes therapy. The PTO alleges, however, that a person having ordinary skill in the art would have been motivated to administer CGP-37157 to treat diabetes, and alleges further that from the teachings of Kennedy such artisan would "reasonably expect" CGP-37157 to increase intramitochondrial Ca2+ level in response to elevated glucose "in an insulin secreting cells (*sic*), *absent evidence to the contrary*." (Action at page 8, lines 16-17, emphasis added)

Applicants respectfully traverse these grounds for rejection. As noted above, the present invention is directed in pertinent part to a method for treating diabetes mellitus, comprising administering, to a subject having or being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity in an insulin secreting cell, wherein the agent has the recited structure according to the amendment submitted herewith, and to related methods.

Applicants traverse the allegation found at page 9, lines 1-14 that applicants' previously submitted arguments constitute "attacking references individually". For reasons previously made of record and also for reasons provided herein, applicants submit that the combination of Kennedy et al. with Cox et al. fails to teach or suggest the instant invention, and that no *prima facie* case of obviousness has been established by the PTO.

Also, as discussed in greater detail below, the PTO improperly relies on a flawed theory whereby the prior art is alleged inherently to suggest that MCA activity would be expected in an insulin secreting cell, when in fact the PTO has failed to meet its burden of establishing any basis in the prior art as evidence to support such a theory.

Specifically, the PTO fails to show that prior to the present application, a person having ordinary skill in the art would have had the requisite reasonable expectation of success in altering intramitochondrial Ca2+ using only an agent that selectively impairs a mitochondrial calcium/ sodium antiporter (MCA) activity in an insulin secreting cell. In particular, and contrary to the assertions found in the Action, the ordinarily skilled artisan would have lacked any reason to believe that of the multiple known channels for Ca2+ transport across the mitochondrial membrane, selectively impairing only the MCA activity in an insulin secreting cell would enhance insulin secretion. The PTO therefore employs impermissible hindsight using the teachings of the present application when it alleges that use of an MCA inhibitor "would be reasonably expected to be useful" for treating diabetes (Action, page 9, lines 12-14).

On this point, applicants submit that the Federal Circuit has held that whether a particular combination of references might be "obvious to try" is not a legitimate test of patentability. *See In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). At most, applicants submit that given the publications cited by the PTO, a person having ordinary skill in the art might have found it "obvious to try" administering an agent that impairs MCA activity in an insulin secreting cell, but such artisan could not have done so with the required "reasonable expectation of success" to arrive at the present invention. The Federal Circuit also held in *In re Fine* that hindsight reconstruction cannot be used to pick and choose among isolated disclosures in the cited references to deprecate the claimed invention. *See In re Fine*, 837 F.2d 1075, 5 USPQ2d 1600. As noted herein, absent such hindsight reconstruction in view of the present application, applicants submit that an ordinarily skilled artisan could not have arrived at the present invention with any reasonable expectation of success.

For reasons also previously made of record, applicants submit that the teachings of Cox et al. are limited to impairment of MCA activity in cardiac tissue (which does not comprise insulin secreting cells) and thus, even when combined with Kennedy et al.—who are

silent with respect to the MCA or any other particular mitochondrial Ca2+ channel—the prior art offers no suggestion of any applicability of an MCA inhibitor to an insulin secreting cell. In response to these arguments, the PTO directs applicants' attention to Gunter et al. (reference AH from the IDS received by the PTO on January 2, 2003) (see Action, page 9, last eight lines and page 10, lines 1-2).

The PTO asserts that Gunter et al. teach dominant MCA activity in heart, skeletal muscle, brain, "and other tissues" while disclosing that a non-MCA mechanism dominates in tissues where magnesium inhibits the Na+-dependent Ca2+ transport mechanism, such as lung and kidney. Gunter et al. fail, however, to teach or suggest which mitochondrial Ca2+ transport activity predominates in insulin secreting cells and consequently the PTO is unable to point to any such disclosure. Merely on the basis of the tissues which are described by Gunter et al., the PTO alleges that a person having ordinary skill in the art "would *expect* MCA activities would be present in any tissues except for . . . lung and kidney" (emphasis added), and that the cited prior art, as a whole, "would render the instant claims obvious, absent evidence to the contrary." The PTO fails, however, to divulge why, in view of the prior art at the time the present application was filed, the ordinarily skilled artisan would have had any greater expectation that in insulin secreting cells an MCA mechanism would predominate instead of a magnesium-inhibitable mechanism or any other Ca2+ transport mechanism.

In further traversal of the allegations made by the PTO, applicants respectfully submit that at the time of filing the present application, the ordinarily skilled artisan would have had absolutely no basis for concluding that the MCA is *necessarily* the predominant Ca2+ transport mechanism in an insulin secreting cell based on the disclosures by Cox et al., by Kennedy et al., by Gunter et al., or anywhere else in the prior art. Moreover, the PTO improperly asserts that the prior art inherently suggests what is in fact a missing piece of evidence–MCA activity in insulin secreting cells—and the PTO errs in alleging that applicants bear the burden of providing "evidence to the contrary". It is well settled that the PTO cannot rely on missing extrinsic evidence from the prior art as being inherently disclosed therein, and that the burden of providing such evidence falls on the PTO, not on applicants. Accordingly, the PTO has failed to meet its burden of establishing that the predominance of MCA activity in

insulin secreting cells is *necessarily* suggested by the prior art, or that the subject matter of the presently claimed invention is inherently suggested in the prior art.

M.P.E.P §2112 provides that:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) (emphasis in original).

Accordingly, Applicants submit that the burden remains with the PTO to supply the requisite basis in fact and/or technical reasoning, where, as Applicants have previously argued, mere conjecture on the part of the PTO (that MCA activity would be "expected" in an insulin secreting cell with no suggestion of such in the art) does not suffice as a finding that the prior art reference contains a disclosure that anticipates or renders obvious the presently claimed invention. Furthermore, the PTO has offered no evidence making clear that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (*Continental Can Co. USA v. Monsanto Co.*,948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)).

According to section 2141.03 of the M.P.E.P.:

> Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1995 (Fed. Cir. 1993).

Also, according to section 2112 of the M.P.E.P.:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1995, 1997 (Fed. Cir. 1993) (emphasis in original).

Further, the M.P.E.P. states that:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact

that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Applicants respectfully submit that the Examiner has not met the burden of making it clear that the missing descriptive matter is necessarily present in the cited prior art. Specifically, the PTO merely raises "probabilities or possibilities" where the Action asserts that "one of ordinary skill in the art would *expect* MCA activities would be present [in an insulin secreting cell]" (emphasis added), but the PTO falls short of establishing that such an expectation could be regarded as reasonable.

Applicants therefore respectfully submit that the Action has not set forth a *prima facie* case of obviousness. As discussed above, the cited references fail to provide a suggestion or motivation for a person having ordinary skill in the art to modify or combine the prior art teachings to arrive at the claimed invention with a reasonable expectation of success. Accordingly, applicants respectfully request that this rejection be withdrawn.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If the Examiner does not believe the claims are allowable for any reason, the Examiner is encouraged to telephone the undersigned at (206) 622-4900.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to Deposit Account No. 19-1090.

Respectfully submitted,

Christen M. Anderson et al.

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Enclosures:
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